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Synthesis and Insecticidal Activity of Novel Pyridine Methanesulfonates*

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Abstract: A model has been developed which has led to the design and synthesis of novel 6-methanesulfonyloxypyridine-2-carboxamides with insecticidal activity, low mammalian toxicity and safety to aquatic organisms. The amides formed from amines with α branching (e.g. isopropyl and *sec*-butyl) demonstrated the highest level of activity. Rice nursery box field test results on laboratory raised insects gave insufficient control of the entire Japanese hopper spectrum to warrant further development of these compounds.

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1 INTRODUCTION

Two classes of acetylcholinesterase inhibitors are used as insecticides, namely organophosphates and carbamates. Relatively less well studied are methanesulfonates. In 1954 Myers and Kemp showed that methanesulfonyl fluoride is an inhibitor of acetylcholinesterase.[1] Since then there have been reports of methanesulfonate esters with utility as either nematocides or insecticides,[2–5] but no compounds of this type have been successfully commercialized.

At the outset of the present work we targeted as a goal the discovery of a rice insecticide. For a compound to be commercially acceptable, as a minimum, it needs to control the four major species (*Nilaparvata lugens* (Staol), *Nephotettix cincticeps* (Uhl), *Laodelphax striatella* (Fall), *Sogatella fucifera* (Horv)) of the Japanese rice hopper complex, to have good mammalian safety ($LD_{50} > 100$ mg kg^{-1}) and low toxicity to aquatic organisms. Particularly of interest to us in this regard was a report of 6-alkylthio-2-pyridyl methanesulfonates (Fig. 1, **I**) with good activity against Japanese rice pests.[6] These compounds were active in addition on insects resistant to organophosphate and carbamate insecticides. Unfortunately these compounds also possessed a high level of acute mammalian toxicity. In our hands 6-isobutylthio-2-pyridyl methanesulfonate (**Ia**) had a rat oral approximate lethal dose (ALD) of 3 mg kg^{-1}.

Kato *et al.*[7] have also reported a strong correlation between the insecticidal activity of the compounds **I** and the acetylcholinesterase inhibition of the corresponding sulfone derivatives (**II**). This result suggests that the active insecticidal form is the sulfone species. In addition Carr *et al.*[8] have disclosed 6-methanesulfonyloxypyridine-2-sulfonamides as insecticides (**III**). From this information we devised a model (**IV**) to help us design compounds for synthesis from which we hoped to obtain compounds with improved properties. This model consists of a nitrogen heterocycle with a methanesulfonate group on one side of the nitrogen atom and on the other side a branched lipophilic side chain containing an oxo-substitution. From this model we conceived of pyridine-2-carboxamides (**V**) as insecticides.

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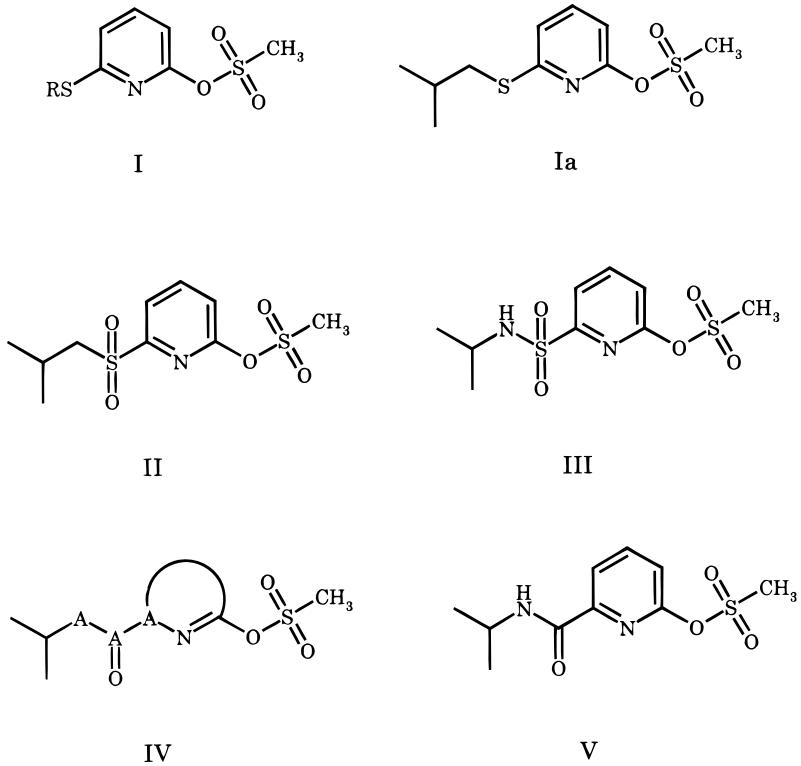


Fig. 1. Structures of compounds discussed.

2 MATERIALS AND METHODS

2.1 Synthesis of compounds

All of the methanesulfonates were prepared by reaction of the hydroxypyridine with methanesulfonyl chloride in the presence of triethylamine in dichloromethane. The 6-hydroxypyridine-2-carboxamides were prepared by activation of the corresponding carboxylic acids with 1,1′-carbonyldiimidazole. Representative procedures are given below.

2.1.1 N-*Isopropyl-6-hydroxypyridine-2-carboxamide*
To a suspension of 6-hydroxypyridine-2-carboxylic acid (20 g, 0·15 mol; Lonza) in tetrahydrofuran (1 litre) was added 1,1′-carbonyldiimidazole (25·9 g, 0·16 mol). This mixture was allowed to reflux for 90 min. After cooling in an ice bath isopropylamine (16 ml, 0·19 mol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The solvent was removed with a rotary evaporator. Dichloromethane and water were added. The product was isolated by filtration. It was dried in a vacuum oven to give 22·5 g of the title compound as a white solid.

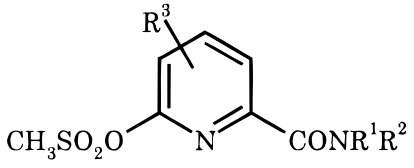
[^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 1·17 (d, 6), 4·03 (m, 1), 5·70 (d, 1), 7·23 (br, 1), 7·68 (dd, 1), 8·18 (br, 1), 11·05 (br, 1).

2.1.2 N-*Isopropyl-6-methanesulfonyloxypyridine-2-carboxamide* (***4***)
To a suspension of *N*-isopropyl-6-hydroxypyridine-2-carboxamide (22·5 g, 0·125 mol) in dichloromethane (625 ml) at 0°C was added triethylamine (24·4 ml, 0·175 mol) followed by dropwise addition of methanesulfonyl chloride (13·6 ml, 0·175 mol). The reaction mixture was stirred at room temperature overnight. It was washed with water, dried (sodium sulfate), filtered and the solvent was removed with a rotary evaporator. The residue was purified by flash chromatography on silica gel (ethyl acetate + hexane (40 + 60 by volume) as eluant) to afford 30·25 g of the title compound as a white solid; m.p. 87–88°C.

[^{1}H]NMR (deuterochloroform): δ 1·29 (d, 6) 3·40 (s, 3), 7·29 (dd, 1), 7·40 (br, 1), 8·00 (dd, 1), 8·19 (d, 1).

2.1.3 N-*Isopropyl-3-chloro-6-methanesulfonyloxypyridine-2-carboxamide* (***25***) *and* N-*Isopropyl-5-chloro-6-methylsulfonyloxypyridine-2-carboxamide* (***26***)
To a solution of *N*-isopropyl-6-hydroxypyridine-2-carboxamide (0·5 g, 2·8 mmol) in chloroform (15 ml) was added *N*-chlorosuccinimide (0·41 g, 3·1 mmol) and benzoyl peroxide (5 mg). The reaction mixture was heated to reflux overnight. The solvent was removed with a rotary evaporator, and the residue was dissolved in dichloromethane (25 ml). After cooling to 0°C, triethylamine (0·55 ml, 3·9 mmol) and methanesulfonyl chloride (0·32 ml, 3·9 mmol) were added. The reaction

TABLE 1
Insecticidal Activity of 6-Methylsulfonyloxypyridine-2-carboxamides



				LD_{90}(*mg litre*$^{-1}$)		
No.	R^1	R^2	R^3	D.u.h.[a]	N.l.[b]	N.c.[c]
1	CH_3	H	H	> 1000	n.d.[d]	n.d.
2	C_2H_5	H	H	520	n.d.	n.d.
3	*n*-C_3H_7	H	H	290	n.d.	n.d.
4	*i*-C_3H_7	H	H	4·7	<2·5	21
5	*cyclo*-C_3H_5	H	H	360	n.d.	n.d.
6	*s*-C_4H_9	H	H	<0·5	<2·5	12
7	(*R*) *s*-C_4H_9	H	H	<0·5	<2·5	<2·5
8	(*S*) *s*-C_4H_9	H	H	22	<2·5	8.1
9	*t*-C_4H_9	H	H	4·5	29	>100
10	*i*-C_4H_9	H	H	>1000	n.d.	n.d.
11	$CH(C_2H_5)_2$	H	H	2·9	<2·5	7·8
12	*t*-C_5H_{11}	H	H	29	n.d.	n.d.
13	$CH(CH_3)CH(CH_3)_2$	H	H	170	<2·5	<2·5
14	$CH(CH_3)CH_2CH_2CH_3$	H	H	11	4·8	48
15	CH_2CH_2F	H	H	210	n.d.	n.d.
16	$CH(CH_3)CH_2CN$	H	H	<0·5	<2·5	7·7
17	$CH(CH_3)CH_2OH$	H	H	>1000	n.d.	n.d.
18	$CH(CH_3)CH_2OCH_3$	H	H	180	<2·5	18
19	$CH(CH_3)SCH_3$	H	H	100	n.d.	n.d.
20	C_2H_5	CH_3	H	5·2	<2·5	7·8
21	*i*-C_3H_7	CH_3	H	55	n.d.	n.d.
22	*s*-C_4H_9	CH_3	H	32	n.d.	n.d.
23	$CH_2CH_2OCH_2CH_2$		H	68	n.d.	n.d.
24	*i*-C_3H_7	H	3-F	59	4·7	44
25	*i*-C_3H_7	H	3-Cl	35	n.d.	n.d.
26	*i*-C_3H_7	H	5-Cl	27	n.d.	>100
27	*i*-C_3H_7	H	5-OCH_3	670	n.d.	n.d.
28	*i*-C_3H_7	H	3-Br	86	n.d.	n.d.
29	*s*-C_4H_9	H	3-Cl	24	6.0	8.0
30	$CH(CH_3)CH_2CN$	H	3-Cl	43	<2·5	7.4

[a] *Diabrotica undecimpunctata howardi.*
[b] *Nilaparvata lugens.*
[c] *Nephotettix cincticeps.*
[d] Not determined.

mixture was allowed to stand at room temperature overnight. It was washed with water, dried (sodium sulfate), filtered and the solvent was removed with a rotary evaporator. The residue was purified by flash chromatography on silica gel (ethyl acetate + hexane (25 + 75 by volume) as eluant) to afford 0·47 g of a mixture of the title compounds as a white solid. This mixture was further purified by HPLC to give 0·27 g of *N*-isopropyl-3-chloro-6-methylsulfonyloxypyridine-2-carboxamide (**25**), m.p. 129°C (eluting first) and 0·10 g of *N*-isopropyl-5-chloro-6-methanesulfonyloxypyridine-2-carboxamide (**26**), m.p. 100–101°C.

3-Chloro isomer: [^{1}H]NMR (deuterochloroform): δ 1·28 (d, 6), 3·46 (s, 3), 4·22 (m, 1). 7·28 (br, 1), 8·00 (d, 1), 8·12 (d, 1).

5-Chloro isomer: [^{1}H]NMR (deuterochloroform): δ 1·28 (d, 6), 3·41 (s, 3), 4·22 (m, 1). 6·98 (br, 1), 7·19 (d, 1), 7·93 (d, 1).

2.2 Insecticidal tests

To measure contact activity, test units, each consisting of a 230 ml plastic cup containing a sprouted corn seed

TABLE 2
Rat Oral Approximate Lethal Dose for Selected 6-Methanesulfonyloxypyridine-2-carboxamides

No.	*ALD* ($mg\ kg^{-1}$)
4	130
6	25
13	≦12
16	25
25	≦25
28	25

were prepared. The test chemical was dissolved in acetone + water (3 + 1 by volume). Sets of three test units were sprayed at six different rates (1000, 250, 50, 10, 2·5, 0·5 mg $litre^{-1}$) by passing the test units on a conveyer belt directly beneath a flat fan hydraulic nozzle. Five third-instar larvae of *Diabrotica undecimpunctata howardi* Barb. were placed into each cup. A moistened dental wick was inserted into each cup to prevent drying and the cups were sealed. The cups were held at 27°C and 50% relative humidity for 48 h, after which time mortality readings were taken. Selected compounds showing good activity in this test were further tested in a systemic test.

To test for systemic activity, the test chemical was dissolved in 10 ml of distilled water. This solution was poured into a conical test unit. Three rice seedlings were then positioned in the unit by a notched sponge disk. The rice seedlings were allowed to absorb the chemical from the solution for 24 h in a growth chamber held at 27°C and 65% relative humidity. Eight to ten third-instar nymphs of *N. lugens* or *N. cincticeps* were transferred into the test units using an aspirator. The test units were held in the growth chamber for 48 h. Counts were taken of the number of live and dead insects. Insects which could not walk were counted as dead.

2.3 Oral approximate lethal dose determinations

The test compound was administered as a single oral dose by intragastric intubation to male rats. The test substance was suspended in acetone + corn oil (15 + 85 by volume) and administered to one rat per dose. The rats were held for 14 days. The ALD was estimated to be the lowest dose at which a rat did not survive the test.

3 RESULTS AND DISCUSSION

Table 1 shows the insecticidal activity for a series of 6-methanesulfonyloxypyridine-2-carboxamides in either a contact test (*D. undecimpunctata howardi*) or a solution systemic test (*N. lugens*, *N. cincticeps*). All compounds tested against the Japanese rice pests were more active against *N. lugens* than *N. cincticeps*. From these data it can be seen that the compounds that most closely fit our model (i.e. contain branching in the amide side chain α to the amine; **4**, **6**, **9** and **11**) had the most activity. Of the *sec*-butyl enantiomers the *R*-enantiomer was more active than the *S*. Additional functionality in the side chain (**15**, **17**–**19**) was not advantageous with the exception of **16**, containing a cyano group, which was highly active. Secondary amides were more active than tertiary ones (**21**–**23**) with the exception of **20** which showed increased activity over **1** and **2**. Additional substituents on the pyridine ring (**24**–**30**) also resulted in compounds with reduced activity.

Table 2 shows rat oral ALD measurements for selected 6-methanesulfonyloxypyridine-2-carboxamides. In general the carboxamides showed much reduced levels of mammalian acute toxicity over the corresponding alkylthio compounds. Compound **4** showed the highest level of safety. A chlorine or bromine atom *ortho* to the carboxamide reduced the level of mammalian safety. These observations suggest that metabolism of the isopropyl carboxamide (which would be more hindered with an *ortho* substituent) may be responsible for the observed level of mammalian safety.

Compound **4** was tested in a 24-h acute static test against *Daphnia magna* Straus and *Pimephales promelas* Raf. (fathead minnow). Against both species the LC_{50} was estimated to be greater than 10 mg $litre^{-1}$ demonstrating an excellent level of aquatic safety.

Field test results in rice (nursery box application, 1·5 g AI per box) using laboratory-raised insects for **4** and **6** were disappointing. Compound **4** gave 14-day control of *N. lugens* and *L. striatella*, but gave little or no control of *N. cincticeps*. Similarly compound **6** gave 28-day control of *N. lugens* and *L. striatella*, but gave little or no control of *N. cincticeps*.

4 CONCLUSIONS

We have developed a model which has helped us design and synthesize 6-methanesulfonyloxypyridine-2-carboxamides with insecticidal activity and improved mammalian safety. While lack of control over the complete spectrum of Japanese rice hoppers prevented the development of these compounds for use in rice, this model should prove useful in designing other insecticidal sulfonates.

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